Current and Future Management of Locally Advanced and Metastatic Prostate Cancer

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With increasing treatment options available, the management of locally advanced and metastatic prostate cancer (PCa) is growing more complex, nuanced, and individualized. Strategies for combining surgery, radiation, chemotherapy, and androgen deprivation therapy (ADT) continue to evolve, as do ADT and immunotherapy options. Additionally, multiple adjunctive agents for metastatic PCa have been recently approved or are pending approval. As the number of locally advanced and metastatic prostate cancers being diagnosed rises, so does the need to consider patients' clinical situations and personal preferences. This review discusses current and potential future approaches to managing locally advanced and metastatic PCa.

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KEY WORDS

Prostate cancer • Metastatic prostate cancer • Locally advanced prostate cancer • Androgen deprivation therapy • Chemotherapy

As diagnostic techniques and treatments for locally advanced and metastatic prostate cancer (PCa) continue to evolve, men with these more advanced prostate cancers are living longer.[1,2] Yet PCa remains the second-leading cause of cancer death among American men.[3]

The National Cancer Institute predicts that in 2020, 191,930 American men will be diagnosed with PCa, and 33,330 men will die of PCa.[4] Since 1999, the rate of PCa incidence per 100,000 American men has fallen from approximately 170 to 109.5,[5] as organizations began advising against routine prostate-specific antigen (PSA) testing in 2008.[6] Although incidence of low-risk prostate cancers fell 37% between 2004 and 2013, incidence of metastatic PCa during those years rose 72%.[7] To help clinicians better understand and navigate the treatment landscape for locally advanced and metastatic PCa, this review assesses present and potential future therapies.

In brief, when selecting non-surgical options for androgen deprivation therapy (ADT), physicians must consider multiple factors, including these drugs' pharmacological profiles, efficacy, and cost. For initial treatment of intermediate- and high-risk localized PCa, guidelines recommend radical prostatectomy (RP) or radiotherapy (RT), with or without ADT. Management of biochemical recurrence (BCR) remains controversial. First-line treatment for newly diagnosed M1 PCa (metastatic hormone-sensitive prostate cancer [mHSPC]) involves ADT alongside guideline considerations for adding approved androgen receptor axis inhibitors as well as docetaxel. For castration-resistant prostate cancer (CRPC), guidelines recommend maintaining castrate testosterone (T) levels through continued ADT.

To discuss current treatments and future concerns in locally advanced and metastatic PCa, the author searched PubMed, meeting abstracts, and clinicaltrials.gov from 1941 through early 2020 using search terms such as *locally advanced prostate cancer (LAPC) guidelines*, *gonadotropin-releasing hormone (GnRH) agonist/antagonist*, *ADT*, and *intermediate, high-risk*, and *metastatic PCa*. The author ultimately selected 102 of the most relevant publications for inclusion in this article.

Results

The vast majority of US cancers—77%, according to National Cancer Institute/Surveillance, Epidemiology, and End Results (NCI/SEER) data (2009-2015)—remain localized at diagnosis, whereas 13% and 6% of PCas have spread to regional lymph nodes and distant sites, respectively.[4] The aggressiveness of initial PCa treatment generally depends on the risk level with which disease presents (Table 1, Table 2).

Therapeutic Goals of ADT

Since Huggins and Hodges first elucidated the androgen-dependent nature of PCa growth, reducing serum testosterone levels through ADT has become the first-line strategy for treating advanced and metastatic disease.[11,12] The American Urological Association (AUA), the National Comprehensive Cancer Network (NCCN), and the European Association of Urology (EAU) all recommend ADT as primary systemic therapy for advanced and metastatic PCa, and in combination with neoadjuvant or adjuvant radiation therapy in localized or locally advanced PCa.[8,13,14] Over the years, the target T level of ADT has arguably evolved from ≤50 ng/dL to below 20 ng/dL based on some association guidelines and consensus papers, suggesting that the latter lower level represents a more effective medical castration.[11]

Non-surgical ADT Options

The variety of treatment options for LAPC and metastatic PCa allows individualization of choices for selecting ADT. Through shared decision-making (SDM), physicians and patients must consider not only clinical factors, but also patients' lifestyles, injection preferences, and compliance factors, along with accessibility and costs.

Widely used non-surgical ADT options include GnRH agonists and GnRH antagonists (Table 3). Popular extended-release formulations allow dosing at intervals ranging from 1 to 12 months.[11]

TABLE 1

Prostate Cancer Risk Stratification

Risk Level	Very Low[a]	Low[a]	Intermediate[b]	High[b]	Very High[b]
Clinical stage	T1c	T1-T2a	T2b-T2c	T3a	T3b-T4
Gleason score (GS)	≤6	≤6	7	8-10	8-10
Prostate-specific antigen (ng/mL)	<10	<10	10-20	>20	>20
Additional findings	<3 cores positive, ≤50% cancer in each core, PSA density <0.15 ng/mL/g				Primary Gleason pattern 5, >4 cores GS 8-10

[a]Must meet all criteria.
[b]Meets any criteria.
Adapted from National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer Version 1.2020[8]; Prostate Cancer Patient Guide.[9]

TABLE 2

International Society of Urological Pathologists Grading System[10]

Risk Group	Grade Group	Gleason Score
Low	1	≤6
Intermediate favorable	2	7 (3 + 4)
Intermediate unfavorable	3	7 (4 + 3)
High	4	8
High	5	9-10

TABLE 3

Pharmacological Profiles of GnRH Agonists and Antagonists

Clinical Parameter	GnRH Agonists	GnRH Antagonists
Initial testosterone (T) surge (which may cause clinical flare)	Yes	No
T suppression onset	3 d	Immediate
Castration achieved	28 d	3-4 d
T microsurges	Yes	No
Follicle-stimulating hormone suppression	Partial	Rapid and sustained
Prostate-specific antigen suppression	Slower through Day 60 ±	Faster in first 2 mo

Adapted from Shore ND et al,[12] Klotz L et al,[15] Crawford ED et al,[18] and McLeod D.[20]

Mechanistically, GnRH agonists bind to GnRH receptors, initially provoking profound stimulation, which leads to substantial increases in GnRH/luteinizing hormone (LH), follicle-stimulating hormone (FSH), and T.[15,16] Sustained overstimulation of the pituitary desensitizes GnRH receptors, thus leading to decreased hormone levels.[17] To block clinical flare symptoms such as urinary obstruction and bone pain stemming from the initial hormonal surge provoked by GnRH agonists, physicians should prescribe a first-generation anti-androgen (bicalutamide, flutamide, or nilutamide) before or along with GnRH agonist therapy (combined androgen blockade [CAB]) and continuing in combination for at least 7 days.[8]

GnRH antagonists block androgen receptors, immediately halting GnRH/LH production. Results include rapid T suppression without an initial hormonal surge, and prolonged suppression without escapes or microsurges as can occur upon re-administration of GnRH agonist doses.[15] Additionally, GnRH antagonists quickly suppress FSH, which contributes to flares associated with GnRH agonist therapy.[16] In the CS21 phase 3 trial, degarelix achieved faster T decline in the first month, superior PSA decline in the first 2 months, and slightly better efficacy in metastatic disease than did leuprolide.[18] However, this trial did not provide evidence to support a short- or long-term advantage of degarelix over leuprolide in patients with BCR. Disadvantages of GnRH antagonists in clinical practice may include their cost, convenience level (only monthly dosing is available), and administration tolerability.[19]

Additional SDM considerations include serum T nadir level.

Increasing evidence indicates that very low T levels may be associated with improved outcomes, including survival.[21-23] Such studies underscore the importance of both monitoring T levels and choosing an ADT that achieves T nadir efficacy.[14]

Adverse events (AEs) associated with ADT also require discussion. In 2010, the US Food and Drug Administration (FDA) and other organizations warned users of GnRH agonists regarding the statistically significant increased risks of diabetes and cardiovascular (CV) events with these drugs, and recommended that physicians evaluate patients for these risk factors.[24,25]

An analysis of six phase 3 trials by Albertsen and colleagues showed that patients treated with degarelix in comparison to an LHRH agonist had a 40% reduction in risk of CV event or death during their first year of ADT.[26] Among patients with preexisting cardiovascular disease (CVD), degarelix-treated patients had an HR of 0.44 for CV (95% confidence interval (CI), 0.26-0.74; $P = 0.002$) event or death. In the first prospective trial to analyze CV outcomes among patients treated with either GnRH agonists or antagonists, Margel and colleagues showed that men in the agonist group experienced more major adverse cardiovascular and cerebrovascular events (MACCE) compared with the GnRH antagonist group (20% vs 3%, respectively; $P = 0.013$).[27]

In the ongoing phase 3 PRONOUNCE trial (NCT02663908), investigators will randomize a total of 900 patients to receive either leuprolide 3-month depot or degarelix monthly for 1 year. The primary endpoint is time from randomization to first confirmed occurrence of the composite MACE endpoint (nonfatal myocardial infarction, nonfatal stroke, or death due to any cause).

The decision to initiate ADT should encompass further detailed discussion with the patient and family regarding the myriad of ADT AEs as well as preventative strategies to diminish or avoid ADT complications.[1,28-31]

Although T monitoring should be standard practice for men on ADT, the optimal timing of T measurement is still debated. A 3- to 6-month interval has been suggested,[14] but the author's clinical experience favors obtaining a baseline T before ADT initiation, then confirming castrate T levels 1 to 3 months following medical or surgical castration. If T >50 (or 20) ng/dL, consider checking GnRH level to differentiate incorrect administration from ineffective castration. If the latter, consider switching to another GnRH agonist/antagonist or bilateral orchiectomy. If T remains elevated, some authors have suggested adding an estrogen or an anti-androgen for further hormonal manipulation, although the clinical benefit remains uncertain.[8]

ADT ± Bone-targeted Therapy

Men who initiate ADT may already be at risk for osteoporosis due to advanced age, hypogonadism, and/or other risk factors.[32] To combat ADT-associated bone loss, the NCCN advises screening and treatment for osteoporosis according to general-population guidelines from the National Osteoporosis Foundation.[33] When fracture risk warrants drug therapy, the NCCN recommends denosumab (60 mg SC every 6 months), zoledronic acid (ZA; 5 mg IV annually), or alendronate (70 mg PO weekly) to boost bone mineral density (BMD).

Clinical Scenarios and Treatment Strategies

Intermediate- and High-risk Localized PCa

Regarding initial treatment, AUA, EAU, and NCCN guidelines recommend RP or RT, with certain caveats, and possible ADT for intermediate- or high-risk PCa (Table 4, Figure 1). NCCN recommendations divide intermediate-risk PCa into favorable (1 intermediate risk factor [IRF], Grade Group 1 or 2, and <50% biopsy cores positive) and unfavorable (2 or 3 IRFs and/or Grade Group 3 and/or ≥50% cores positive) strata.

Radiation With Adjuvant ADT

ADT is recommended in patients with unfavorable intermediate- and high-risk PCa considering RT.[36,37] Neoadjuvant therapy with a GnRH agonist often reduces overall prostate volume by 25% to 33% within 3 months,[38,39] a finding that supports the common practice of beginning ADT 2 to 3 months before starting radiation. Many studies have shown benefits for the combination of radiation with short-term ADT.[40-45]

Additional studies support use of radiation and long-term ADT in combined populations of intermediate- and high-risk local PCa.[46-52] Although Level I evidence supports ADT for all intermediate-risk disease, compelling retrospective and post hoc evidence suggests that favorable intermediate-risk disease may be treated adequately with RT alone.[53]

RT in High-risk PCa

Approaches to high-risk localized PCa using adjuvant systemic therapies have remained relatively unchanged for the past few decades.[54] For patients with nodal metastases, standard-of-care approaches include adjuvant ADT, based largely on the trial by Messing and colleagues.[55] Neoadjuvant or adjuvant ADT is also considered

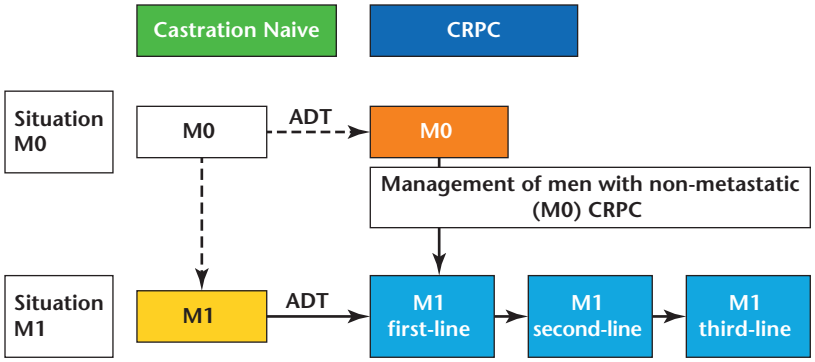

Figure 1. Disease states and strategies.[34] ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer.

TABLE 4

Initial Treatment Recommendations for Intermediate- and High-risk Local Prostate Cancer[8,14,35]

Organization	Intermediate Risk		High Risk
AUA/ ASTRO/ SUO	Favorable or unfavorable: RP or RT + ADT		RP or RT + ADT
EAU	RP if life expectancy >10 y, only as part of multimodal therapy ePLND if estimated metastatic risk >5% EBRT + ADT (4-6 months) with low-dose brachytherapy boost		RP if life expectancy >10 y, only as part of multimodal therapy ePLND EBRT + long-term ADT (2-3 y)
NCCN	Favorable	Unfavorable	If life expectancy >5 y or symptomatic: EBRT + ADT (1.5-3 y) EBRT + brachytherapy + ADT (1-3 y) RP + PLND: If adverse features without LN metastases: EBRT ± ADT (6 mo) or observation If LN metastasis: ADT ± EBRT, or observation
	If life expectancy >10y: Active surveillance EBRT or brachytherapy alone RP ± PLND if predicted probability of LN metastases ≥2%: Adverse features without LN metastases: EBRT ± ADT (6 mo) or observation LN metastasis: ADT ± EBRT, or observation	Life expectancy >10y: RP ± PLND if predicted probability of LN metastases 2%: Adverse features without LN metastases: EBRT ± ADT (6 mo) or observation LN metastases: ADT (category 1) ± EBRT, or observation EBRT ± ADT (4 mo)	
	If life expectancy <10 y: Observation (preferred) EBRT or brachytherapy alone	Life expectancy <10 y: Observation (preferred) EBRT + brachytherapy ± ADT (4 mo)	

ADT, androgen deprivation therapy; ASTRO, American Society for Radiation Oncology; AUA, American Urological Association; EAU, European Association of Urology; EBRT, external beam radiotherapy; ePLND, extended pelvic lymph node dissection; LN, lymph node; NCCN, National Comprehensive Cancer Network; RP, radical prostatectomy; RT, radiotherapy; SUO, Society of Urologic Oncology.

standard in high- and intermediate-risk PCa being treated with RT, although optimal ADT duration has not been established.[53]

Current recommendations for using radiation with long-term ADT in high-risk PCa are based partly on trials showing cancer-specific and overall survival (OS) benefits for 28 to 36 months of ADT in patients with locally advanced disease.[49,56] These findings led to 2010 NCCN guideline changes and clinical-practice changes to include 2 to 3 years of ADT for high-risk PCa.[57]

Considering the AEs associated with ADT, shortening long-term ADT may be desirable. Although the PCS IV phase 3 trial showed an overall survival hazard ratio (OSHR) of 1.02 for 18 versus 36 months ADT,[58] it remains unclear whether these results support a conclusion that 18 months ADT is noninferior to 36 months because the trial did not use a noninferiority design. However, Yang and colleagues reported that an HR near 1.0, with a relatively narrow CI, raises the likelihood that the OS difference between 18 and 36 months for this population is small. These authors therefore suggested that these emerging data raise the possibility that 18 months may be sufficient for select high-risk patients.[53]

RP Plus ADT

AUA/American Society for Radiation Oncology (ASTRO)/Society of Urologic Oncology (SUO) and EAU guidelines recommend against using neoadjuvant ADT for localized PCa in patients who have chosen RP outside of clinical trials.[14,36]

Moderate evidence suggests that 6 to 8 months of neoadjuvant ADT before RP provides clinical benefit (usually lower positive margin rates after RP and decreased PSA recurrence risk after 2-5 years), but no studies have demonstrated an OS benefit.[59] Conversely, evidence including a meta-analysis of 11,149 patients[60] shows that long-term ADT immediately after RP can benefit men with high-risk localized PCa, particularly those with positive lymph nodes.[59]

BCR

BCR definitions differ slightly depending on primary treatment and guideline authors. The EAU and AUA define post-RP relapse as PSA >2 ng/mL, and post-RT >2 ng/mL above nadir (or, for the AUA, 3 consecutive PSA increases).[61,62] Because patients with PSA recurrence after primary RP or RT have different risks of subsequent symptomatic metastatic disease, physicians should carefully interpret BCR endpoints when considering treatment initiation, for example, ADTs.[14]

Once PSA relapse is diagnosed, physicians must determine as accurately as possible whether the recurrence has occurred locally or distantly. Initial clinical and pathologic factors of the recurrence (T category, PSA, and Gleason score) and PSA kinetics (PSA doubling time [PSADT] and interval to PSA failure) help determine the risk of subsequent metastases and PCa-specific mortality (PCSM).[14] For specific recommendations regarding BCR after surgery, radiation, high-intensity focused ultrasound (HIFU), or cryoablation and after primary surgery with adjuvant radiation or after localized salvage failure, please see Figures 2, 3, and 4.

The management of BCR following primary curative treatment remains controversial, partly because PSA-only recurrence does not consistently correlate with either PCa-specific or overall survival.[63] Recommendations regarding post-RP recurrence

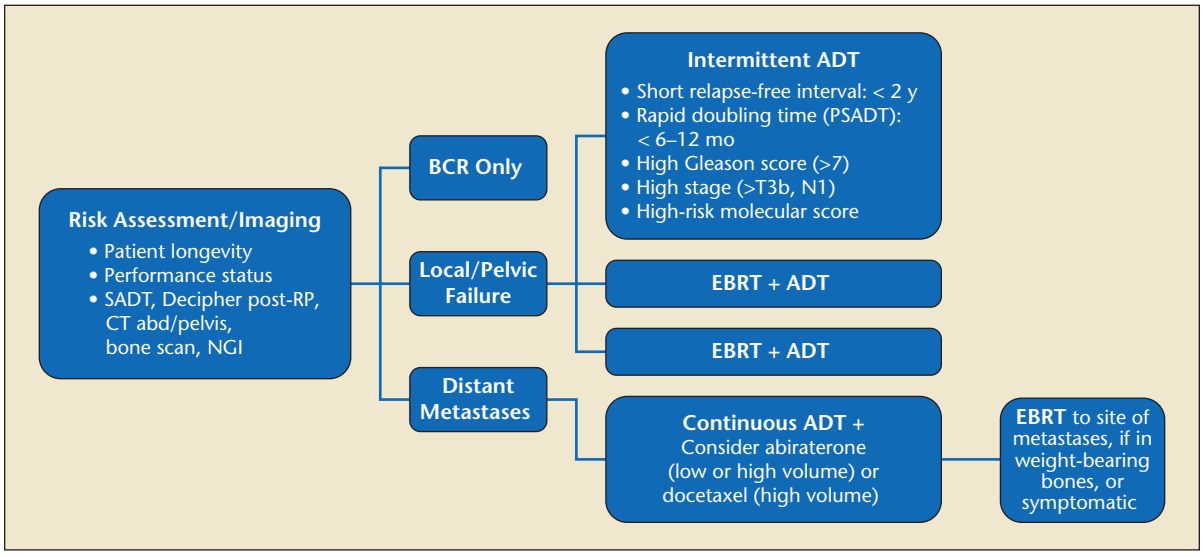

Figure 2. Primary failure after surgery (PSA >0.2). ADT, androgen deprivation therapy; BCR, biochemical recurrence; EBRT, external beam radiotherapy; NGI, next-generation imaging; PSA, prostate-specific antigen; RP, radical prostatectomy; SADT, salvage androgen deprivation therapy.

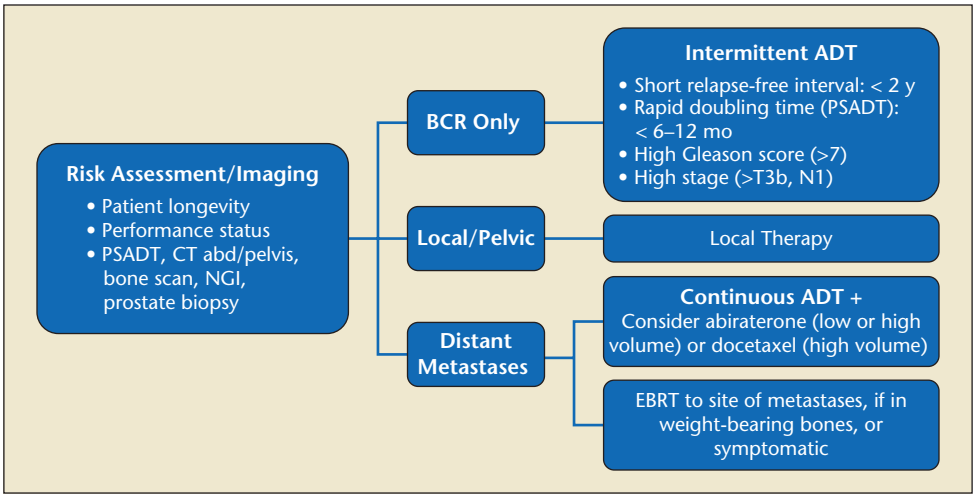

Figure 3. Radiation, HIFU, cryoablation failure (PSA2 + Nadir).[103] ADT, androgen deprivation therapy; BCR, biochemical recurrence; EBRT, external beam radiotherapy; NGI, next-generation imaging; PSA, prostate-specific antigen; PSADT, PSA doubling time.

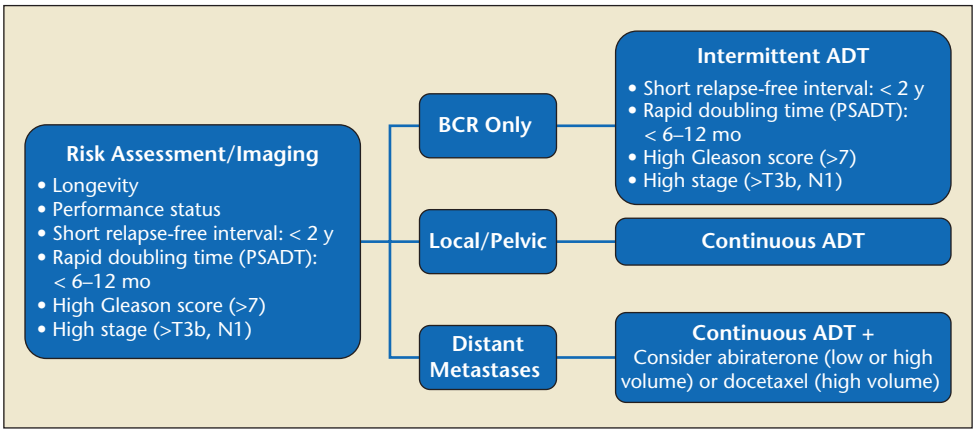

Figure 4. Primary failure after surgery (PSA >0.2).[103] ADT, androgen deprivation therapy; BCR, biochemical recurrence; PSA, prostate-specific antigen; PSADT, PSA doubling time.

illustrate subtle differences between guidelines. For example, the EAU strongly recommends treating patients with a PSA rise from undetectable using salvage radiotherapy (SRT), but not offering hormonal therapy to every pN0 patient treated with SRT. AUA guidelines state that clinicians should offer ADT to patients being treated with SRT after RP failure (PSA ≥0.20 ng/mL).[64] For low-risk BCR, the EAU strongly recommends offering androgen suppression (AS) and possibly delayed SRT. In 10-year follow-up of the GETUG-AFU 16 trial, progression-free survival for patients treated with RT plus short-term goserelin (10.8 mg on the first day of RT and 3 months later) was 64%, versus 49% for patients treated with radiotherapy alone (HR 0.54; 95% CI, 0.43-0.68; stratified log-rank test, $P < 0.0001$). These authors concluded with a recommendation for AS plus RT as salvage treatment in patients with rising PSA concentration after RP.[65]

For BCR after RT, options include ADT or local procedures such as salvage RP, cryotherapy, interstitial brachytherapy, and HIFU, but weak evidence makes firm recommendations impossible.[14] Ongoing phase 3 trials may help guide future practice in BCR (Table 5).

Newly Diagnosed Metastatic PCa

Median OS for patients who present with mHSPC (Table 6) is approximately 42 months.[66] Upon conventional radiographic imaging detecting M1 disease, the clinicians' therapeutic selection choices are now numerous.[67]

EAU guidelines strongly recommend treating both symptomatic and asymptomatic M1 patients (or discussing deferred castration with well-informed patients). The first-line treatment for newly diagnosed M1 PCa is ADT.[66] No Level I evidence favors a specific type of ADT, except in patients with impending spinal-cord compression, for whom either bilateral orchiectomy or GnRH antagonists are preferred, per the EAU (albeit with a "weak" recommendation).[14] Offer surgical or medical castration alone (with or without an anti-androgen) only to patients unfit for or uninterested in newer combinations including

TABLE 5

Ongoing Phase 3 Trials in Biochemical Recurrence

Trial	Objectives	Estimated Completion
RADICALS (NCT00541047)	Assess timing of RT and use of ADT in conjunction with postoperative radiotherapy Determine the impact of RT on quality of life	September 2021
RAVES (NCT00860652)	Compare adjuvant RT vs active surveillance with early salvage RT in post-RP patients with positive margins and/or pT3 disease	December 2026

ADT, androgen deprivation therapy; RP, radical prostatectomy; RT, radiotherapy.

TABLE 6

Treatment Recommendations for Newly Diagnosed Metastatic Hormone-sensitive Prostate Cancer

National Comprehensive Cancer Network	European Association of Urology	
GnRH agonist + first-generation anti-androgen (nilutamide, flutamide, bicalutamide) ± docetaxel GnRH agonist + abiraterone GnRH antagonist ± docetaxel GnRH antagonist ± abiraterone Orchiectomy ± abiraterone	Immediate systemic treatment (ADT) for symptomatic or asymptomatic disease Orchiectomy or ADT + docetaxel if fit enough for chemotherapy Surgery and or local radiotherapy if evidence of impending complications such as spinal cord compression or bone fracture Castration + abiraterone + prednisone if fit enough for this regimen	Strong
	No anti-androgen monotherapy LHRH antagonists, especially if impending spinal cord compression or bladder outlet obstruction Short-term anti-androgens for patients treated with LHRH agonist to reduce risk of flare	Weak

ADT, androgen deprivation therapy.

either docetaxel or abiraterone acetate plus prednisone.[66]

ADT in mHSPC

ADT remains the gold standard in mHSPC, regardless of metastatic volume (low vs high) with Level I evidence for combining treatments (docetaxel, abiraterone, apalutamide), according to NCCN, EAU, and ESMO guidelines.[8,14,68] To avoid castration-dependent pharmacokinetics of docetaxel, physicians commonly start docetaxel 6 to 12 weeks after initiating ADT.

Adding the second-generation AR signaling inhibitor (ASI) abiraterone acetate to ADT represents another standard of care.[69] In the LATITUDE and STAMPEDE trials, this combination produced nearly identical OS improvements of 38% (HR 0.62 and 0.63, respectively).[70,71]

The phase 3 TITAN trial showed that apalutamide plus ADT significantly improved

radiographic progression-free survival (rPFS) and OS versus placebo plus ADT in patients with metastatic castration-sensitive PCa.[72] In September 2019, the FDA approved apalutamide for use in this population.[73] In mid-2019, NCCN guidelines added apalutamide as a category 1 option for M1 castration-naive PCa.[8] Additionally, the FDA granted priority review for enzalutamide in mHSPC based on positive results of the ARCHES and ENZAMET phase 3 trials. The ARCHES phase 3 trial showed that at median of 14.4 months, ADT plus enzalutamide significantly improved rPFS over ADT plus placebo.[74] In ENZAMET, HR for death in the enzalutamide group was 0.67 (95% CI, 0.52-0.86; $P = 0.002$) versus ADT alone at a median follow-up of 34 months.[75]

Four-year follow-up of STAMPEDE, moreover, showed that ADT plus upfront docetaxel or abiraterone produced no significant differences between these two regimens in median OS, metastasis-free survival (MFS), or PCa-specific survival.[76] Because castrated patients clear docetaxel roughly twice as quickly as un-castrated patients,[77] do not delay docetaxel until patients become castration resistant.[78] Clinicians continue to debate which treatment to add to ADT, and then how to best sequence the next line of therapy.

In selecting which combination for high-volume mHSPC patients, guidelines do not recommend either abiraterone or docetaxel over the other. In high-volume mHSPC, there is unequivocal OS benefit to ADT with docetaxel versus ADT alone,[70] according to NCCN and ASCO guidelines.[8,79] In low-volume mHSPC, a recent analysis of STAMPEDE results revealed that docetaxel confers additive benefits regardless of metastatic burden—5-year OS in the low-burden group specifically was 72%, versus 57% for ADT alone ($P = 0.107$).[80] ADT plus abiraterone also represents a reasonable standard of care irrespective of metastatic burden.[68]

In low-volume mHSPC, NCCN and ESMO 2019 guidelines recommend RT to the prostate for patients without contraindications to radiotherapy. ADT is also required, unless medically contraindicated. In a section of the STAMPEDE trial, however, adding radiotherapy to standard care in patients with low metastatic burden improved failure-free survival but not OS.[81] EAU guidelines recommend (although weakly) offering castration plus RT to patients whose first presentation is M1 disease, with low volume as defined by CHAARTED criteria.

For patients with metastasis at first presentation (versus relapse/metastases after definitive local therapy), EAU guidelines cite that docetaxel or abiraterone should be consider as standard therapy in conjunction with ADT.[14] However, ASCO recommends ADT plus abiraterone strongly in high-risk de novo mHSPC and moderately in lower-risk cases.[79]

CRPC

Regardless of ADT modality, nearly all patients with advanced PCa maintained on ADT eventually develop castration resistance, requiring changes in therapeutic strategy. In all patients with rising PSA and/or clinical progression, physicians must evaluate serum T to confirm castrate resistance before considering treatments.[13] In CRPC, continuing ADT to maintain castrate T levels (≤20 ng/dL) is strongly recommended and considered the standard of care in both metastatic and nonmetastatic CRPC.[8,14,82]

In deciding which patients to evaluate for metastatic disease, the EAU suggests using baseline PSA, PSA velocity, and PSADT, which have been associated with time to first bone metastasis, bone MFS, and OS.[83,84] The PROSPER and SPARTAN phase 3 trials in high-risk M0 CRPC showed significant MFS benefits for enzalutamide (HR for metastasis or death vs placebo, 0.29) and apalutamide (HR 0.28), respectively.[85,86] In the ARAMIS trial, median MFS for patients on darolutamide was 40.4 months, versus 18.4 months for placebo (HR for metastasis or death with darolutamide, 0.41; $P < 0.001$).[87] NCCN, EAU, and AUA guidelines also offer recommendations regarding treatments such as abiraterone, docetaxel, sipuleucel-T, and bone-targeting therapies in mCRPC decision-making.[8,14,82]

Intermittent Androgen Deprivation Therapy (IADT)

Another clinical option involves stopping ADT in well-informed and requesting patients who have had a strong PSA response (usually defined as PSA <1 ng/dL in metastatic and relapsing disease) yet have significant tolerability concerns.[14] Patients should undergo examinations every 3 to 6 months and those without evidence of progression should resume ADT if PSA rises above an empirically chosen threshold (subjectively designated in various trials, 10-20 ng/dL).[11,14] Allowing T levels to recover between treatment cycles may reduce ADT-associated AEs (Figure 5).[11]

Studies in locally advanced, relapsing, and metastatic PCa suggest that IADT is noninferior to continuous ADT (CADT) while offering potentially fewer side effects and better quality of life.[88-91] However, not all IADT studies show clear advantages over continuous

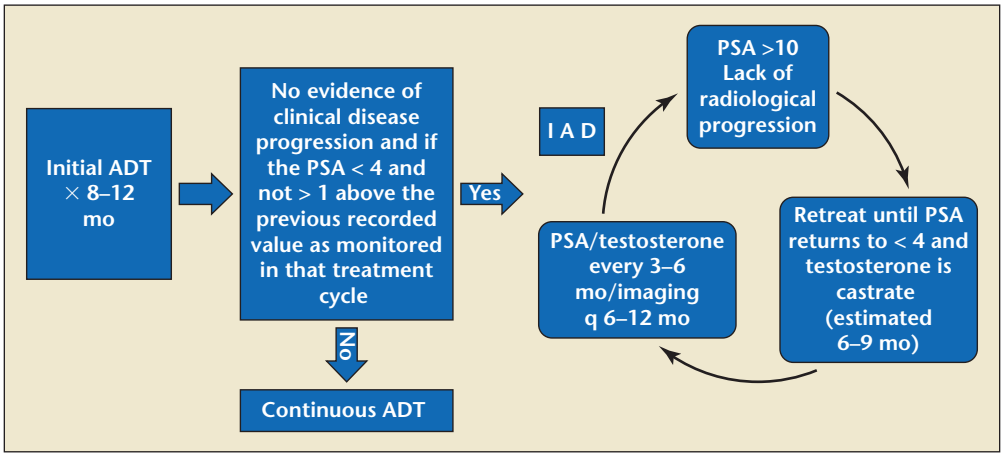

Figure 5. Intermittent androgen deprivation therapy (IADT) pathway.[12,14] ADT, androgen deprivation therapy; PSA, prostate-specific antigen; PSADT, PSA doubling time.

CADT. Most IADT trials show only modest reductions in AEs during off-treatment phases.[92] The ICELAND trial showed no significant differences between IADT and CADT in health-related quality of life or AEs.[93]

EAU and NCCN guidelines note that although IADT appears to reduce sexual and other side effects of CADT, the largest trial addressing IADT in M1b patients (SWOG 9346) failed to demonstrate noninferiority to CADT.[94] Additionally, a recent analysis of a large metastatic PCa trial revealed an increased risk of CV events for patients on IADT.[95]

Ideal IADT candidates have yet to be defined. NCCN guidelines say IADT may be allowed to reduce toxicity in M0 castration-naive patients with PSA persistence or recurrence after RP or EBRT, or those with castration-naive M1 PCa.[8] The EAU recommends offering IADT only to well-informed patients with significant ADT AEs who had strong PSA responses to ADT induction (PSA <4 ng/mL in metastatic disease).[14]

Metastasis-directed Therapy (MDT)

Oligometastatic PCa denotes an intermediate state between localized disease and widespread metastases, marked by a limited number of metastases (usually 3-5).[96] By targeting metastases directly, MDT could potentially delay the need for systemic treatment in patients relapsing after local therapy; however, no data suggest an OS improvement for MDT.[14] Research regarding optimal strategies for oligometastatic PCa are lacking, and MDT remains experimental. However, numerous clinical MDT trials are ongoing.[97]

Discussion

Presently, ADT remains the gold standard for advanced PCa. Regarding the combination of ADT with chemotherapy and/or novel AR antagonist therapy in mHSPC, several ongoing trials will help determine ideal treatment sequencing (Table 7).

However, growing awareness of ADT side effects and availability of novel hormonal agents—along with healthcare payers' concern for value-based care—are impacting the treatment landscape for therapeutic selections.

Although the 2010 warnings from the FDA, AUA, and other organizations regarding the need to evaluate baseline cardiovascular risk in patients being considered for ADT have had less impact than expected, ADT usage appears to be shifting. One study showed that compared with 2008 through 2009, patients with low-risk PCa were significantly less likely to receive ADT in 2011 through 2012 (10.0% vs 14.7%; $P < 0.001$).[98] In the same study, patients with intermediate-risk disease were slightly less likely to receive ADT post-2010 (33.4% vs 35.1%; $P < 0.001$), and patients with high-risk PCa were slightly more likely to undergo ADT after 2010 (71.1% vs 66.8%; $P < 0.001$).

Among hormonal agents, 150 mg bicalutamide (now generic) is used for LAPC in the EU and elsewhere, as either adjuvant therapy or a monotherapeutic alternative to surgical or medical castration.[99] The oral drug relugolix, now under FDA review, may allow for a once-daily GnRH antagonist. Relugolix phase 3 results have recently been published.[100]

Meanwhile, the rise in publications examining T replacement for men who have or have had PCa reflects patients' and providers' interest in minimizing consequences of T suppression.[101,102] Immunotherapy trials and other drug-targeted pathways in development may someday obviate the need for ADT for

TABLE 7

Ongoing Androgen Deprivation Therapy Plus Chemotherapy Trials

Study	Phase	Estimated Primary Completion
Docetaxel Before Degarelix in Newly Diagnosed Metastatic Prostate Cancer (NCT03069937)	2	February 2020
PEACE1 (A Phase III Study for Patients with Metastatic Hormone-Naïve Prostate Cancer; NCT01957436)	3	2020
S1216 (ADT + TAK-700 vs ADT + Bicalutamide for Metastatic Prostate Cancer; NCT01809691)	3	March 2022
ARASENS (ODM-201/Darolutamide in Addition to Standard ADT and Docetaxel in Metastatic Castration Sensitive Prostate Cancer; NCT02799602)	3	August 2022
STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; NCT00268476)	2/3	September 2024
Arm A (control: ADT + radiotherapy ± docetaxel ± abiraterone)		
Arm C (ADT + docetaxel + prednisolone)		
Arm E (ADT + zoledronic acid + docetaxel + prednisolone)		
Arm G (ADT + abiraterone + prednisolone)		
Arm J (ADT + abiraterone + enzalutamide + prednisolone)		

select advanced PCa populations. Examples include SNS-301 (Sensei Biotherapeutics Inc., Gaithersburg, MD) and the novel nanoparticle vaccine candidate INO-5150 (Inovio Pharmaceuticals Inc., Plymouth Meeting, PA), both presently in phase 2. The role of small-molecule or antibody-delivered targeted alpha therapy, which can reach prostate-specific membrane antigen–expressing tumors regardless of metastatic location, may hold promise.[103] Also, there is continued interest in MDT to avoid or delay ADT.[93,104]

Conclusions

The understanding and application with which physicians apply ADT will continue to evolve with new combinatorial approaches and better understanding of AE management. Additional research exploring these combinations and sequencing strategies, as well as the evaluation of novel ADT options and potential alternative approaches, is ongoing and will continue to require educational awareness. ■

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MAIN POINTS

- In recent years, incidence of high-risk prostate cancer (PCa) has risen, largely in response to various organizations' 2008 recommendation to avoid routine prostate-specific antigen (PSA) testing.
- The landscape of treatments for locally advanced and metastatic PCa continues to expand, as does awareness of treatment side effects and the need to tailor shared decision-making processes to each patient's clinical situation, personal preferences, and lifestyle.
- Among non-surgical androgen deprivation therapy (ADT) options, the choice between GnRH agonists and antagonists rests on multiple factors, including these drugs' pharmacological profiles, clinical efficacy, cost, and convenience. A 2010 US Food and Drug Administration (FDA) recommendation to assess baseline cardiovascular (CV) risk in men being considered for GnRH agonist therapy reflects a growing concern over such side effects.
- For initial treatment of intermediate- and high-risk localized PCa, American Urological Association (AUA), European Association of Urology (EAU), and National Comprehensive Cancer Network (NCCN) guidelines recommend radical prostatectomy (RP) or radiotherapy (RT), with caveats, with or without ADT. The NCCN recommends ADT for men with high-risk and unfavorable intermediate-risk PCa considering RT. Studies support use of neoadjuvant ADT as well as long-term ADT in appropriate clinical situations.
- Management of biochemical recurrence (BCR) remains controversial, as PSA-only recurrence does not consistently correlate with either overall or PCa-specific survival.
- First-line treatment for newly diagnosed M1 PCa is ADT; no Level I evidence favors a specific form of ADT, except in cases with impending spinal-cord compression, for which the EAU prefers either bilateral orchiectomy or GnRH antagonists. Additionally, ADT represents the gold standard in metastatic hormone-sensitive prostate cancer (mHSPC), irrespective of metastatic burden; Level I evidence also supports combining ADT with treatments including docetaxel, abiraterone, and apalutamide. Based on results of the ARCHES and ENZAMET phase 3 trials, the FDA has granted priority review status to enzalutamide in mHSPC.
- In castrate-resistant prostate cancer (CRPC), whether metastatic or nonmetastatic, continuing ADT to maintain castrate testosterone (T) levels is strongly recommended by multiple organizations. Enzalutimide, apalutamide, and darolutamide have demonstrated positive results in CRPC.

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